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General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

ARTICLES

1 **Single-channel properties of human NaV1.1 and mechanism of channel dysfunction in SCN1A-associated epilepsy.** Carlos G. Vanoye, Christoph Lossin, Thomas H. Rhodes, and Alfred L. George Jr.

15 **Intracellular pH modulates taste receptor cell volume and the phasic part of the chorda tympani response to acids.** Vijay Lyall, Hampton Pasley, Tam-Hao T. Phan, Shobha Mummalaneni, Gerard L. Heck, Anna K. Vinnikova, and John A. DeSimone

35 **Effects of multiple metal binding sites on calcium and magnesium-dependent activation of BK channels.** Lei Hu, Huanghe Yang, Jingyi Shi, and Jianmin Cui

51 **Proton sensing of CLC-0 mutant E166D.** Sonia Traverso, Giovanni Zifarelli, Rita Aiello, and Michael Pusch

67 **Regulation of connexin hemichannels by monovalent cations.** Miduturu Srinivas, D. Paola Calderon, Jack Kronengold, and Vytas K. Verselis

Cover picture: Single-channel recordings from heterologously expressed recombinant human wild-type SCN1A (NaV1.1) channels demonstrate occasional late openings and brief periods of increased P_o consistent with infrequent entry into a slower gating mode. An epilepsy-associated mutation (R1648H) generates persistent current by inducing more late openings and higher basal P_o without further gating mode shifts (see article by Vanoye et al., 1–14).

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MEETING SUMMARY

77 **The 59th symposium of the Society of General Physiologists. Na,K-ATPase and related cation pumps: structures, mechanisms, and diseases. (Organized by David Gadsby, Jack Kaplan, and Jerry Lingrel).** Lawrence G. Palmer

COMMENTARIES

89 **Functions of stretch activation in heart muscle.** Kenneth B. Campbell and Murali Chandra

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95 **Activation dependence of stretch activation in mouse skinned myocardium: implications for ventricular function.** Julian E. Stelzer, Lars Larsson, Daniel P. Fitzsimons, and Richard L. Moss

109 **Gating of acid-sensitive ion channel-1: release of Ca^{2+} block vs. allosteric mechanism.** Ping Zhang, Fred J. Sigworth, and Cecilia M. Canessa

119 **Direct observation of a preinactivated, open state in BK channels with β2 subunits.** G. Richard Benzinger, Xiao-Ming Xia, and Christopher J. Lingle

133 **Different transport mechanisms in plant and human AMT/Rh-type ammonium transporters.** Maria Mayer, Gabriel Schaaf, Isabelle Mouro, Claude Lopez, Yves Colin, Petra Neumann, Jean-Pierre Cartron, and Uwe Ludewig

145 **Identification of a disulfide bridge linking the fourth and the seventh extracellular loops of the Na^+/glucose cotransporter.** Dominique G. Gagnon, Pierre Bissonnette, and Jean-Yves Lapointe

159 **Membrane-delimited inhibition of maxi-K channel activity by the intermediate conductance Ca^{2+}-activated K channel.** Jill Thompson and Ted Begenisich

171 **Mini-dystrophin expression down-regulates overactivation of G protein–mediated IP3 signaling pathway in dystrophin-deficient muscle cells.** Haouaria Balghi, Stéphane Sebille, Bruno Constantin, Sylvie Patri, Vincent Thoreau, Ludivine Mondin, Elise Mok, Alain Kitzis, Guy Raymond, and Christian Cognard

183 **Distinct populations of HCN pacemaker channels produce voltage-dependent and voltage-independent currents.** Catherine Proenza and Gary Yellen

191 **Structural determinants for functional coupling between the β and α subunits in the Ca^{2+}-activated K^+ (BK) channel.** Patricio Orio, Yolima Torres, Patricio Rojas, Ingrid Carvacho, Maria L. Garcia, Ligia Toro, Miguel A. Valverde, and Ramon Latorre

205 **A Na^+- and Cl^--activated K^+ channel in the thick ascending limb of mouse kidney.** Marc Paulais, Sahran Lachheb, and Jacques Teulon

217 Acknowledgment

219 Correction

Cover picture: (Left) During depolarization, the activation of DHPRs, followed by calcium release from RyRs (fast) would also stimulate PLCs through Gi protein. The produced IP3 reaches IP3Rs on the SR and leads to calcium release (slow). (Right) The mini-dystrophin protein would repress the activity of PLC via the Gi protein and reduce the release from IP3Rs (see article by Balghi et al., 171–182).

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COMMENTARIES

221 **On the loose: uncaging Ca^{2+}-induced Ca^{2+} release in smooth muscle.** Gregory C. Amberg, Manuel F. Navedo, and Luis F. Santana

ARTICLES

225 **Ca^{2+}-induced Ca^{2+} release through localized Ca^{2+} uncaging in smooth muscle.** Guangju Ji, Morris Feldman, Robert Doran, Warren Zipfel, and Michael I. Kotlikoff

237 **EGFR kinase regulates volume-sensitive chloride current elicited by integrin stretch via PI-3K and NADPH oxidase in ventricular myocytes.** David M. Browe and Clive M. Baumgarten

253 **Differential sialylation modulates voltage-gated Na^+ channel gating throughout the developing myocardium.** Patrick J. Stocker and Eric S. Bennett

267 **Interaction of acid-sensing ion channel (ASIC) 1 with the tarantula toxin psalmotoxin 1 is state dependent.** Xuanmao Chen, Hubert Kalbacher, and Stefan Gründer

277 **Time-dependent block and resurgent tail currents induced by mouse $\beta 4_{154-167}$ peptide in cardiac Na^+ channels.** Ging Kuo Wang, Thomas Edrich, and Sho-Ya Wang

291 **Effects of tetracaine on voltage-activated calcium sparks in frog intact skeletal muscle fibers.** Stephen Hollingworth, W. Knox Chandler, and Stephen M. Baylor

309 **Role of charged residues in the S1–S4 voltage sensor of BK channels.** Zhongming Ma, Xing Jian Lou, and Frank T. Horrigan

329 **On the interaction of neomycin with the slow vacuolar channel of *Arabidopsis thaliana*.** Joachim Scholz-Starke, Armando Carpaneto, and Franco Gambale

341 **Access of extracellular cations to their binding sites in Na,K-ATPase: role of the second extracellular loop of the α subunit.** Oihana Capendeguy, Pierre Chodanowski, Olivier Michielin, and Jean-Daniel Horisberger

353 **Correction**

Cover picture: Ca^{2+} sparks evoked by two photon flash photolysis in smooth muscle. Top images show confocal linescan recording during repeated exposure of a urinary bladder myocyte to 730 nm laser illumination (red bars). At the bottom, a similar experiment shows a decrease in delay to Ca^{2+} release in FKBP12.6 knockout cells (see article by Ji et al., 225–235).

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COMMENTARIES

355 **Shedding light on cones.** Barry E. Knox and Eduardo Solessio

ARTICLES

359 **Physiological features of the S- and M-cone photoreceptors of wild-type mice from single-cell recordings.** Sergei S. Nikonov, Roman Kholodenko, Janis Lem, and Edward N. Pugh Jr.

375 **A single P-loop glutamate point mutation to either lysine or arginine switches the cation–anion selectivity of the CNGA2 channel.** Wei Qu, Andrew J. Moorhouse, Meenak Chandra, Kerrie D. Pierce, Trevor M. Lewis, and Peter H. Barry

391 **Voltage-dependent gating rearrangements in the intracellular T1–T1 interface of a K^+ channel.** Guangyu Wang and Manuel Covarrubias

401 **Functional roles of charged amino acid residues on the wall of the cytoplasmic pore of Kir2.1.** Yuichiro Fujiwara and Yoshihiro Kubo

421 **TRPM7 channel is regulated by magnesium nucleotides via its kinase domain.** Philippe Demeuse, Reinhold Penner, and Andrea Fleig

435 **Roles of K149, G352, and H401 in the channel functions of ClC-0: testing the predictions from theoretical calculations.** Xiao-Dong Zhang, Yong Li, Wei-Ping Yu, and Tsung-Yu Chen

449 **Mechanism of β4 subunit modulation of BK channels.** Bin Wang, Brad S. Rothberg, and Robert Brenner

Cover picture: (Left) Confocal image of mouse retinal section revealing cones expressing EGFP, overlaid on DIC image. (Right) Traces show responses of several "inner segments" drawn together into a suction pipette; the outer segments were stimulated with 500-nm light steps of graded intensity and a superimposed 361-nm flash. The response to the UV flash originates in a cone (see article by Nikonov et al., 359–374).

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ARTICLES

467 **The polyamine binding site in inward rectifier K^+ channels.** Harley T. Kurata, Laurence J. Marton, and Colin G. Nichols

481 **Access of quaternary ammonium blockers to the internal pore of cyclic nucleotide-gated channels: implications for the location of the gate.** Jorge E. Contreras and Miguel Holmgren

495 **Feedback network controls photoreceptor output at the layer of first visual synapses in *Drosophila*.** Lei Zheng, Gonzalo G. de Polavieja, Verena Wolfram, Musa H. Asyali, Roger C. Hardie, and Mikko Juusola

511 **Coupling modes and stoichiometry of Cl^-/HCO_3^- exchange by slc26a3 and slc26a6.** Nikolay Shcheynikov, Youxue Wang, Meeyoung Park, Shigeru B.H. Ko, Michael Dorwart, Satoru Naruse, Philip J. Thomas, and Shmuel Muallem

525 **Functional characterization of homo- and heteromeric channel kinases TRPM6 and TRPM7.** Mingjiang Li, Jianmin Jiang, and Lixia Yue

539 **Voltage clamp fluorometric measurements on a type II Na^+-coupled P_i cotransporter: shedding light on substrate binding order.** Leila V. Virkki, Heini Murer, and Ian C. Forster

557 **Relationship between pore occupancy and gating in BK potassium channels.** Rebecca A. Piskorowski and Richard W. Aldrich

577 **The light peak of the electroretinogram is dependent on voltage-gated calcium channels and antagonized by bestrophin (Best-1).** Lihua Y. Marmorstein, Jiang Wu, Precious McLaughlin, John Yocom, Mike O. Karl, Rudgar Neussert, Soenke Wimmers, J. Brett Stanton, Ronald G. Gregg, Olaf Strauss, Neal S. Peachey, and Alan D. Marmorstein

591 **Soluble mediators, not cilia, determine airway surface liquid volume in normal and cystic fibrosis superficial airway epithelia.** Robert Tarran, Laura Trout, Scott H. Donaldson, and Richard C. Boucher

Cover picture: Kinetic scheme for the NaPi-II transport cycle based on voltage clamp fluorometry (top). The largest change in fluorescence (ΔF) is associated with occupancy of states 1 and 8. Simulated ΔF in response to membrane voltage and Na^+ ions (left), when replotted as a function of [Na] reflects cooperative binding of 2 Na^+ ions (right) (see article by Virkki et al., 539–555).

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COMMENTARIES

605 **Plasmalemmal Ca^{2+} signaling in arterial smooth muscle: it's elementary!.** Ian Parker

ARTICLES

611 **Mechanisms underlying heterogeneous Ca^{2+} sparklet activity in arterial smooth muscle.** Manuel F. Navedo, Gregory C. Amberg, Madeline Nieves, Jeffery D. Molkentin, and Luis F. Santana

623 **Calcium release domains in mammalian skeletal muscle studied with two-photon imaging and spot detection techniques.** José Gómez, Patricia Ñeco, Marino DiFranco, and Julio L. Vergara

639 **Electrogenic NA/HCO_3 cotransporter (NBCe1) variants expressed in *Xenopus* oocytes: functional comparison and roles of the amino and carboxy termini.** Suzanne D. McAlear, Xiaofen Liu, Jennifer B. Williams, Carmel M. McNicholas-Bevensee, and Mark O. Bevensee

659 **The antibacterial activity of human neutrophils and eosinophils requires proton channels but not BK channels.** Jon K. Femling, Vladimir V. Cherny, Deri Morgan, Balázs Rada, A. Paige Davis, Gabor Czirják, Peter Enyedi, Sarah K. England, Jessica G. Moreland, Erzsébet Ligeti, William M. Nauseef, and Thomas E. DeCoursey

673 **Calcium-dependent gating of MthK, a prokaryotic potassium channel.** Brittany Zadek and Crina M. Nimigean

687 **Membrane stretch slows the concerted step prior to opening in a Kv channel.** Ulrike Laitko, Peter F. Juranka, and Catherine E. Morris

703 **Block of muscle nicotinic receptors by choline suggests that the activation and desensitization gates act as distinct molecular entities.** Yamini Purohit and Claudio Grosman

719 **Estimating binding affinities of the nicotinic receptor for low-efficacy ligands using mixtures of agonists and two-dimensional concentration–response relationships.** Yamini Purohit and Claudio Grosman

737 **Calmodulin contributes to gating control in olfactory calcium-activated chloride channels.** Hiroshi Kaneko, Frank Möhrlen, and Stephan Frings

COMMUNICATIONS

749 **Ca^{2+}-activated Cl^- current from human bestrophin-4 in excised membrane patches.** Takashi Tsunenari, Jeremy Nathans, and King-Wai Yau

TUTORIAL RESEARCH ARTICLES

755 **Statistical limits to the identification of ion channel domains by sequence similarity.** Anthony A. Fodor and Richard W. Aldrich

767 Correction

768 Correction

Cover picture: Action potential–evoked Ca^{2+} release domains in mouse skeletal muscle fibers shown in three-dimensional perspectives (top left, and bottom) and as a contour map (top right). The plots were created by juxtaposing $\Delta F/F$ fluorescence transients from 78 consecutive spot positions (100 nm apart) along the fiber axis and spanning approximately three sarcomeres (see article by Gómez et al., 623–637).